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Original article

The clinical usefulness of carotid ultrasonography in patients with an inconclusive exercise treadmill stress test result

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ABSTRACT

Background: Although a treadmill exercise stress testing (EST) is often the first-line screening procedure for subjects with an intermediate probability of coronary artery disease (CAD), one limitation of this test is the high rate of inconclusive tests that result from borderline exercise-induced ST changes. The carotid intima media thickness (CIMT) correlates well with atherosclerosis. The purpose of this study was to evaluate the clinical usefulness of performing CIMT measurements in patients with an inconclusive EST.
Methods: Symptomatic patients without history of vascular disease and with inconclusive EST result were included. Inconclusive results were defined as the presence of horizontal or downsloping ST-segment depression between 0.5 and 0.9 mm or 1.0 and 1.4 mm upsloping ST-segment depression. After inconclusive EST regarding electrocardiographic changes, the measurements of the CIMT and myocardial perfusion imaging study (MPS) were performed in all patients. The CIMT was measured at the posterior wall of the common carotid artery. The diagnosis of CAD was based on the presence of reversible perfusion defects on exercise MPS.
Results: A total of 87 patients (57 men) with a mean age of 58.9 ± 7.2 years were enrolled. The MPS was positive in 18 patients. The CIMT in patients with positive MPS was significantly greater than in patients with negative MPS. The CIMT was 0.82 ± 0.33 mm in patients with positive MPS and 0.63 ± 0.21 mm in patients with negative MPS ($p = 0.004$). Receiver operating characteristic curve analyses revealed that the greatest specificity was obtained when the cut-off value of CIMT was set at 0.66 mm (sensitivity 39%; specificity 72.5%; positive predictive value 27%; negative predictive value 82%).
Conclusion: In patients with inconclusive electrocardiographic changes during EST, CIMT was a useful measurement to prevent alternative more expensive and invasive tests. Additionally, mean CIMT is useful for screening patients with an inconclusive EST result to exclude CAD.

Introduction

Exercise treadmill stress testing (EST) is a useful diagnostic tool for primary assessment of symptomatic patients with an intermediate probability of coronary artery disease (CAD) based on clinical findings [1]. However, one limitation is the high rate of nondiagnostic tests. EST results have been classified as negative (no evidence of reversible ischemia), positive (moderately or severely abnormal), or equivocal (reported as nondiagnostic, suboptimal, equivocal, possibly artifactual or minimally abnormal) [2]. While the most determined reason for the high rate of nondiagnostic tests that result from patients' failure to reach the target heart rate, another reason results from inconclusive electrocardiographic abnormalities. In case of nondiagnostic EST, patients are referred for more expensive and invasive stress tests and consequently, it causes prolonged hospital evaluation [3].

Carotid intima media thickness (CIMT) measurement has been used as a surrogate index of atherosclerosis. Several studies have found an association between increased CIMT and the incidence of cardiovascular disease in the general population [4–7]. Exercise testing and arterial ultrasonography are able to improve significantly the accuracy of the risk stratification over conventional risk factors [8].

The purpose of this study was to evaluate the clinical usefulness of performing CIMT measurements in patients with an inconclusive stress test.

Methods

Patient population

The study population consisted of patients referred to an outpatient clinic with stable chest pain and suspected CAD. The sample

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comprised 87 (57 male, mean age 58.9 ± 7.2 years) consecutive symptomatic patients with no previous history of overt atherosclerotic disease (cerebral, peripheral, or CAD, which was defined as any degree of CAD on previous angiogram or history of myocardial infarction or angina) who underwent exercise test with an 'inconclusive' result. Age ranged from 36 to 74 years.

A complete history was taken and a physical examination [measurement of weight, height, body mass index (BMI) and systolic and diastolic blood pressure in the supine position after 10 min rest] and 12-lead electrocardiography (ECG) at rest were performed. Blood samples were taken for fasting blood glucose and cholesterol level.

After the medical examination, patients with an intermediate pretest probability of CAD on the basis of gender, age, and symptoms (nonangina, atypical angina, or typical angina) were prepared for treadmill exercise stress testing (EST) for evaluation of symptoms of possible coronary artery disease [9].

Patients with a history of stroke, unstable angina pectoris, myocardial infarction, peripheral artery disease, valvular disease, arrhythmia, abnormal ECGs that would preclude adequate interpretation of changes or taking digoxin were excluded. Patients were excluded if they were pregnant or lactating women. Since the extent of CAD may be underestimated when calcium channel blockers and β blockers are given, these medications were discontinued for 48 h.

Informed consent was obtained from each patient. The study protocol was approved by the ethical committee of the hospital.

Treadmill exercise stress testing

EST was performed using a modified Bruce protocol exercise treadmill test. The protocol for EST has been previously reported [9,10]. Briefly, modified Bruce protocol was employed. Since our institution uses a heart rate of at least 85% of the adjusted age-predicted maximal heart rate (220 beats/min-age) to indicate adequate stress, the patients were encouraged to continue until 85% of maximal heart rate was achieved. All participants reached this 85% target. During exercise, a 12-lead ECG and blood pressure were recorded at the end of each 3-min stage and at peak exercise. Postexercise ECGs were obtained after 5 min. Based on clinical or ECG response, the test was considered as normal (negative), ischemic (positive), and inconclusive.

The EST was considered ischemic if there was horizontal or downsloping ST-segment depression of at least 1.0 mm or 1.5 mm upsloping ST-segment depression, 80 ms after the J point in ≥1 lead was observed. However, in the presence of horizontal or downsloping ST-segment depression from 0.5 to 0.9 mm or 1.0 to 1.4 mm upsloping ST-segment depression, the test was considered as 'inconclusive.' Patients with 'inconclusive' ECG findings were assessed.

Besides the ECG findings, blood pressure response to exercise is an important finding. Hypertensive blood pressure response was defined as systolic blood pressure of >220 mmHg and/or a diastolic blood pressure of >95 mmHg.

Myocardial perfusion imaging study

Eighty-seven subjects with an 'inconclusive' treadmill EST were referred for exercise myocardial perfusion single-photon emission tomography (SPECT) imaging. Studies were performed using the treadmill (Series 2000 Treadmill; GE Marquette Medical Systems, Milwaukee, WI, USA) according to a Bruce protocol. The isotope used was 99 mTc (technetium)-sestamibi. At 1 min before peak exercise, the stress dose of sestamibi was injected intravenously. The patient exercised for at least 1 min longer after the injection. Stress and rest studies were performed using a 1-day protocol "one-day rest/stress Tc-99m protocols" for exercise stress according to the consensus report [11]. Resting and peak exercise 99mTc sestamibi injection with perfusion imaging was performed using a gamma camera (Infia; H300WE, VC [GE Medical System, Tirat Hacarmel, Israel]). A positive test was defined as the presence of one or more reversible perfusion defects during stress.

Measurement of carotid intima-media thickness

All carotid ultrasonographic examinations were performed with the same device (Logic S8; GE Medical Systems) equipped with an 8-MHz linear probe. Patients were examined in the supine position with the head 45° away from the side being scanned.

Digital images were stored directly from the ultrasound system. Far-wall CIMTs were measured in the distal of each carotid artery in the proximal 1 cm of carotid bulb in areas free of plaque using B-mode imaging [12]. Measurements were repeated three times and results were averaged. Mean CIMT values from the far walls of the right and left common carotid arteries were reported. Plaque was defined as focal wall being 50% thicker than the surrounding wall. Presence of any calcification, plaque, and echocardiographically lucent components was noted.

Statistical analysis

Categorical and numeric variables are expressed in percentage and mean ± standard deviations respectively. Numerical variables were tested with Mann–Whitney *U*-test, and categorical variables were tested using Fisher's exact test or Chi-square test whichever was suitable. Spearman's test was used for correlation analysis. Sensitivity and specificity values for positive MPS were calculated from receiver operating characteristic curve (ROC). A *p*-value of <0.05 was regarded significant for all analyses. All the statistical tests were done using SPSS 11.5 (SPSS Inc., Chicago, IL, USA).

Reproducibility

Intra- and interobserver reproducibilities were assessed for CIMT values. For intraobserver variability, the same operator performed a second measurement more than a month after the initial analysis. The Bland–Altman analysis for interobserver reproducibility [mean difference – 95% confidence interval (CI)] and intraobserver reproducibility [intraclass correlation coefficient (ICC), 95% CI] were calculated. The interobserver and intraobserver reproducibility showed a perfect agreement for the CIMT – interobserver and intraobserver agreement were assessed as 0.04 (−0.09 to 0.11) and [(0.92), (0.89–0.94)], respectively.

Results

A total of 87 patients (males, 65.5%) with a mean age of 58.9 (±7.2) years who had an intermediate pretest probability (10–90%) of CAD based on age, gender, and nature of symptoms were included. Among them, 59 patients had hypertension, 25 dyslipidemia, 55 were smokers, and 21 had diabetes mellitus. Baseline characteristics of the study population are shown in Table 1.

After inconclusive EST regarding ECG changes, the measurements of CIMT and myocardial perfusion imaging study (MPS) were performed in all patients.

All ultrasound examinations (100%) provided images good enough to allow the measurement of the CIMT. We did not observe any calcification or plaque. Mean CIMT was found to be 0.67 ± 0.25 mm.

Coronary artery disease was diagnosed based on the MPS. The MPS was positive in 18 (21%) of the 87 patients. Patients with pathologic results of the perfusion study had a borderline difference in levels of low-density lipoprotein cholesterol and age (for both,

Table 1
Baseline characteristics of patients.

$n = 87$	Number (%)	Mean	SD
Age (years)		58.9 (36–74)	7.2
Men	57 (65.5)		
Height		166.5	9.3
Weight		73.7	10.4
Body mass index (kg/m^2)		26.5	1.8
Hypertension	59 (67.8)		
Dyslipidemia	25 (28.7)		
Diabetes mellitus	21 (24.1)		
Smokers	55 (63.3)		
Family history of premature coronary disease	32 (36.8)		
Medication use			
Statins	25 (28.7)		
β blockers	17 (19.5)		
Angiotensin inhibitors	46 (52.9)		
Calcium channel blockers	28 (32.2)		
Heart rate		69.5	8.9
Systolic BP		145.5	20
Diastolic BP		76.8	12.4
Mean CIMT (mm)		0.67	0.25

Values are means ± SD or numbers of patients (percentages).
BP, blood pressure; CIMT, carotid intimal-media thickness; SD, standard deviation.

$p = 0.05$) (Table 2). The MPS-positive patients had a higher blood pressure response ($p = 0.001$). The CIMT in patients with positive MPS was significantly greater than in patients with negative MPS. The CIMT was 0.82 ± 0.33 mm in patients with positive MPS and 0.63 ± 0.21 mm in patients with negative MPS ($p = 0.004$) (Fig. 1).

By Spearman correlation analysis, there was a significant moderate correlation between CIMT and level of total cholesterol, systolic blood pressure, and advanced age (for all, $p < 0.001$) (Table 3).

In order to determine cut-off value of CIMT for the prediction ability of positive MPS, ROC curves were plotted for mean CIMT. The analysis showed that the greatest specificity was obtained when the cut-off value of CIMT was set at 0.66 mm (sensitivity 39%; specificity 72.5%; positive predictive value 27%; negative predictive value 82%) (Fig. 2).

In the setting of an inconclusive EST result, presence of CIMT < 0.66 mm predicted the absence of perfusion defects (consequently CAD) diagnosed by MPS (negative predictive value 82%).

Table 2
Characteristics of myocardial perfusion imaging study (MPS) positive and negative patients.

	MPS (+) $n = 18$	MPS (−) $n = 69$	p-Value
Age (years)	61.8 ± 7.3	58.2 ± 7	0.05
Men	9 (50)	48 (69)	0.12
Height	168.7 ± 10.6	166 ± 8.9	0.27
Weight	75.7 ± 10.5	73.2 ± 10	0.35
Body mass index (kg/m^2)	26.5 ± 0.82	26.4 ± 1.95	0.92
Hypertension	15 (83.3)	44 (63.7)	0.11
Systolic BP	151.4 ± 18.2	144 ± 20.1	0.16
Diastolic BP	76.6 ± 11.6	76.9 ± 12.7	0.92
Heart rate	71.1 ± 9.4	69.1 ± 8.8	0.39
Diabetes mellitus	5 (28)	16 (25)	0.69
Total cholesterol (mg/dl)	241 ± 7 9	218 ± 60	0.19
LDL-cholesterol (mg/dl)	148.2 ± 35.3	129 ± 36.8	0.05
HDL-cholesterol (mg/dl)	39.8 ± 16.8	36 ± 11.3	0.37
Family history of premature coronary disease	4 (22.2)	28 (41)	0.15
Smokers	13 (72)	42 (61)	0.37
Type of ST-segment changes (%)-(I/II/III)	61/22/17	61/29/10	0.68
Hypertensive BP response	12 (67)	15 (22)	0.001
Mean CIMT (mm)	0.82 ± 0.33	0.63 ± 0.21	0.004

Values are number (%). BP, blood pressure; CIMT, carotid intimal-media thickness; LDL, low-density lipoprotein; HDL, high-density lipoprotein.
Type of ST-segment changes I/II/III represent upslope, horizontal, downslope, respectively.

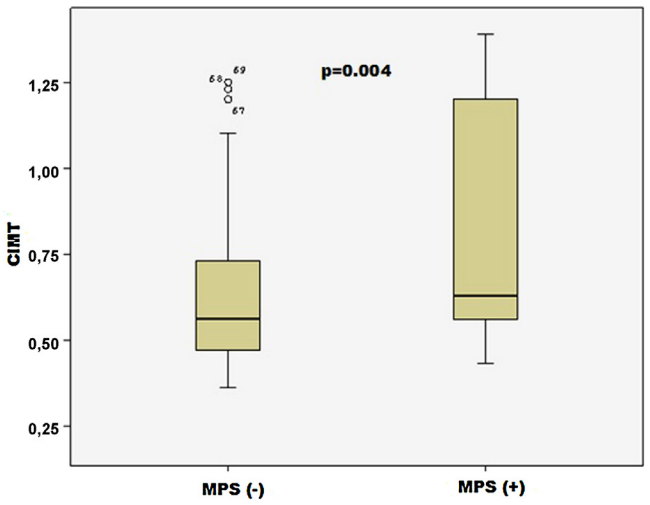

Fig. 1. Distribution of the intima-media thickness in myocardial perfusion imaging study positive and negative patients. MPS, myocardial perfusion imaging study; CIMT, carotid intima media thickness.

Table 3
The correlation analysis of carotid intima-media thickness and risk factors.

	CIMT	
	r	p
Total cholesterol	0.415	<0.001
Systolic BP	0.406	<0.001
Age	0.430	<0.001

BP, blood pressure; CIMT, carotid intimal-media thickness.

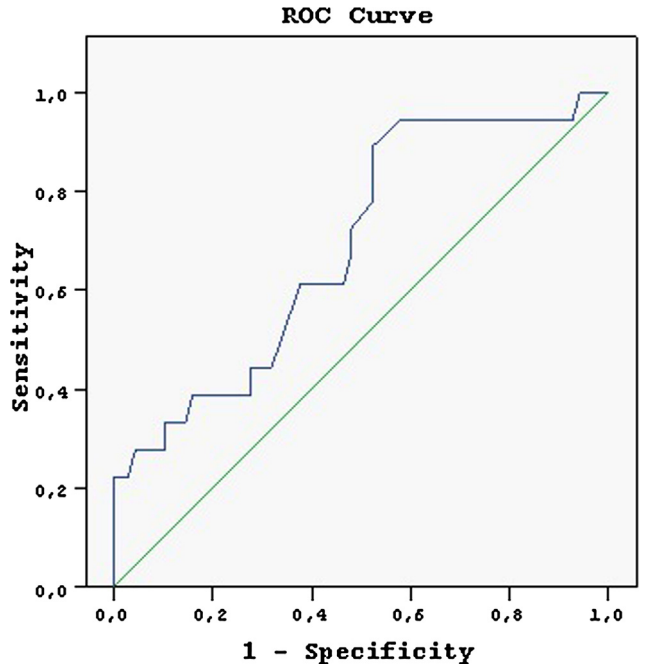

Fig. 2. Receiver operating characteristic (ROC) curve analysis to identify positive myocardial perfusion imaging study. The cut-off value of mean carotid intima-media thickness was set at 0.66 mm.

No specific ECG changes in the EST were found to predict the outcome of the MPS. However, hypertensive blood pressure response was more prevalent in subjects with a pathologic perfusion study.

Discussion

In this study, we prospectively examined the predictive value of CIMT for the presence of perfusion defects diagnosed by MPS in symptomatic patients after inconclusive EST.

The CIMT in the present study was greater in the group of patients with positive MPS. We found CIMT measurement as 0.82 ± 0.33 mm in MPS positive patients. This finding was similar to the literature. Adams et al. [13] reported CIMT measurement as 0.83 ± 0.20 mm in patients with CAD. Additionally, we found the mean of the CIMT measurement in the MPS negative patient group was 0.63 ± 0.21 mm.

The results of the present study are in line with a previous study [14], which showed that CIMT was increased in older subjects with asymptomatic myocardial ischemia as evidenced by exercise ECG alone or in combination with thallium scan. Another study conducted by O'Leary et al. [15] stated that there was a positive association between CIMT measured from common carotid artery and the presence of CAD in elderly patients. However, Heuten et al. [16] could not find a correlation between CIMT and the presence of reversible perfusion defects on exercise MPS. Interestingly, they reported that either CIMT measurement or classic risk factors could not improve the diagnostic value of stress ECG.

Additionally, we investigated the cut-off level of mean CIMT for identifying the presence of perfusion defect. In the setting of an inconclusive EST result, when the cut-off value of mean CIMT set at 0.66 mm, for patients whose mean CIMT was below this cut-off level, we might predict the absence of CAD (negative predictive value 82%). Recently, a published a report showed a cut-off level of maximum CIMT for identifying severe CAD [17]. They found that the greatest sensitivity and specificity were obtained when the cut-off value of maximum CIMT was set at 2.45 mm. However, our proposed cut-off value was smaller. Some particularities of the studies should be emphasized. First, the technique used to measure the CIMT is different. Irie et al. [17] measured the intima-media thickness (IMT) of the common carotid artery, of the carotid bulb and of the internal carotid artery and they calculated the mean of the measurements. Furthermore, they measured the greatest thickness of IMT (including plaque lesions) from the same points of artery and the greatest value of them was defined as maximum IMT. In our study, we used the method according to the consensus report [12]. Secondly, while their study group included only type 2 diabetic subjects and those with positive results for noninvasive tests referred to coronary computed tomography angiography or conventional coronary angiography, our study comprised a heterogenous population and used MPS for the diagnosis of CAD.

Previously, it has been shown that CIMT measurements can be useful in risk stratification of symptomatic patients undergoing EST. Kanwar et al. [2] showed that carotid ultrasound can be applied to stratify the patients with absence of plaque showing a negative predictive value (100%). However, they studied a small number (10 patients) of patients with an equivocal/negative EST result and no carotid plaque.

In this study, we preferred treadmill exercise to dipyridamole stress, since the image quality with treadmill exercise was superior to dipyridamole stress images with higher ratios of myocardial uptake [18]. Dipyridamole appears to be as accurate as exercise SPECT. Nevertheless, a meta-analysis of diagnostic test performance has summarized evidence documenting that the sensitivity of exercise electrocardiography is significantly lower than that of myocardial perfusion SPECT [19]. Myocardial perfusion SPECT imaging with Tc-99m-sestamibi had 90% sensitivity and 80% specificity for the detection of angiographically significant (more than 50% stenosis) CAD [20].

Patients with diabetes and high BMI may have an increased probability for nondiagnostic EST [21]. In this study, while 21 patients had diabetes mellitus, overall subjects had high BMI value (26.5 ± 1.8 kg/m^2). Additionally, high low-density lipoprotein cholesterol levels and advanced age were more prevalent in patients with positive MPS.

In the present study, we found that patients with positive MPS had significantly higher systolic blood pressure than those with negative MPS. During EST, abnormal systolic blood pressure response and poor exercise capacity were predictive of poor prognosis [22,23]. Clinicians should take into account blood pressure response to exercise as an additional risk stratification.

Limitations

Several limitations of this study should be discussed. First, this study consisted of a relatively small number of subjects. However, the incidence of inconclusive EST based on ECG findings is relatively low. Additionally, long-term follow-up results in a large number of patients who have CIMT <0.66 mm and do not undergo further tests may be required. Second, we used MPS for further noninvasive test instead of multidetector computed tomography (MDCT). Although MDCT has high diagnostic accuracy in multiple patient subgroups, because of its known limitations (cost, iodine contrast use, not applicable widely), MDCT cannot be performed in all patients. We believe that MDCT is an important tool in higher risk groups such as patients with known CAD and who have undergone previous revascularization interventions. However, while measures obtained by carotid ultrasonography and coronary MDCT are correlated, they each assess different aspects of atherosclerosis. MDCT can detect significant coronary stenosis in patients based on the direct assessment of coronary anatomy, whereas, MPS permits evaluation of the relationship of perfusion to regional function. Additionally, besides indication for the assessment of the presence, location, extent, and severity of myocardial ischemia, MPS is used to determine the significance of anatomic lesions detected by angiography. Third, the diagnosis of CAD was based on the presence of reversible perfusion defects on exercise MPS. MPS is most useful in patients with an intermediate likelihood of angiographically significant CAD (defined as $\geq$50% reduction of the coronary lumen diameter) based on age, sex, symptoms, risk factors, and the results of stress testing [20]. Finally, the values for specificity 72.5% and negative predictive value 82% may not be high as a clinical diagnostic tool in the general population. Therefore, the clinical utility of CIMT as a screening tool should be verified in studies with larger sample size. Especially, the cut-off level of CIMT should be confirmed by further studies.

In conclusion, in patients with an intermediate probability of CAD and inconclusive ECG changes during EST, CIMT was a useful tool to prevent alternative more expensive and invasive tests. Additionally, mean CIMT is useful for screening patients with an inconclusive EST result to exclude CAD.

Conflicts of interest

The author declares that there are no conflicts of interest to disclose.

References

[1] Livschitz S, Sharabi Y, Yushin J, Bar-On Z, Chouraqui P, Burstein M, Eldad A. Limited clinical value of exercise stress test for the screening of coronary artery disease in young, asymptomatic adult men. Am J Cardiol 2000;86:462–4.

[2] Kanwar M, Rosman HS, Fozo PK, Fahmy S, Vikraman N, Gardin JM, Bess RL, Cohen GI. Usefulness of carotid ultrasound to improve the ability of stress testing to predict coronary artery disease. Am J Cardiol 2007;99:1196–200.
[3] Diercks DB, Kirk JD, Amsterdam EA. Can we identify those at risk for a non-diagnostic treadmill test in a chest pain observation unit. Crit Pathw Cardiol 2008;7:29–34.
[4] Holaj R, Spacil J, Petrasek J, Malik J, Haas T, Aschermann M. Intima-media thickness of the common carotid artery is the significant predictor of angiographically proven coronary artery disease. Can J Cardiol 2003;19:670–6.
[5] Calmarza P, Trejo JM, Lapresta C, Lopez P. Lack of association between carotid intima-media thickness and apolipoprotein (a) isoforms in a sample of Spanish general population. J Cardiol 2013;61:372–7.
[6] Altekin ER, Koç S, Karakaş MS, Yanıkoğlu A, Başarıcı I, Demir I, Alpsoy E. Determination of subclinical atherosclerosis in plaque type psoriasis patients without traditional risk factors for atherosclerosis. Turk Kardiyol Dern Ars 2012;40:574–80.
[7] Bernard S, Sérusclat A, Targe F, Charrière S, Roth O, Beaune J, Berthezène F, Moulin P. Incremental predictive value of carotid ultrasonography in the assessment of coronary risk in a cohort of asymptomatic type 2 diabetic subjects. Diabetes Care 2005;28:1158–62.
[8] Cournot M, Taraszkiewicz D, Cambou JP, Galinier M, Boccalon H, Hanaire-Broutin H, Chamontin B, Carrié D, Ferrières J. Additional prognostic value of physical examination, exercise testing, and arterial ultrasonography for coronary risk assessment in primary prevention. Am Heart J 2009;158:845–51.
[9] Gibbons RJ, Balady GJ, Bricker JT, Chaitman BR, Fletcher GF, Froelicher VF, Mark DB, McCallister BD, Mooss AN, O'Reilly MG, Winters WL, Gibbons RJ, Antman EM, Alpert JS, Faxon DP, et al. ACC/AHA 2002 guideline update for exercise testing: summary article. J Am Coll Cardiol 2002;40:1531–40.
[10] Lewis WR, Amsterdam EA, Turnipseed S, Kirk JD. Immediate exercise testing of low risk patients with known coronary artery disease presenting to the emergency department with chest pain. J Am Coll Cardiol 1999;33:1843–7.
[11] Henzlova MJ, Cerqueira MD, Mahmarian JJ, Yao SS. Stress protocols and tracers. J Nucl Cardiol 2006;13:e80–90.
[12] Stein JH, Korcarz CE, Hurst RT, Lonn E, Kendall CB, Mohler ER, Najjar SS, Rembold CM, Post WS, American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Endorsed by the Society for Vascular Medicine. J Am Soc Echocardiogr 2008;21:93–111.
[13] Adams MR, Nakagomi A, Keech A, Robinson J, McCredie R, Bailey BP, Freedman SB, Celermajer DS. Carotid intima-media thickness is only weakly correlated with the extent and severity of coronary artery disease. Circulation 1995;92:2127–34.
[14] Nagai Y, Metter EJ, Earley CJ, Kemper MK, Becker LC, Lakatta EG, Fleg JL. Increased carotid artery intimal-medial thickness in asymptomatic older subjects with exercise-induced myocardial ischemia. Circulation 1998;98:1504–9.
[15] O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson Jr SK. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. N Engl J Med 1999;340:14–22.
[16] Heuten H, Claeys M, Goovaerts I, Ennekens G, Bosmans J, Vrints C. Can measurement of the intima-media thickness of the carotid artery improve the diagnostic value of exercise stress tests. Acta Cardiol 2006;61:501–5.
[17] Irie Y, Katakami N, Kaneto H, Nishio M, Kasami R, Sakamoto K, Umayahara Y, Sumitsuji S, Ueda Y, Kosugi K, Shimomura I. The utility of carotid ultrasonography in identifying severe coronary artery disease in asymptomatic type 2 diabetic patients without history of coronary artery disease. Diabetes Care 2013;36:1327–34.
[18] Chow BJ, Ananthasubramaniam K, dekemp RA, Dalipaj MM, Beanlands RS, Ruddy TD. Comparison of treadmill exercise versus dipyridamole stress with myocardial perfusion imaging using rubidium-82 positron emission tomography. J Am Coll Cardiol 2005;45:1227–34.
[19] Fleischmann KE, Hunink MG, Kuntz KM, Douglas PS. Exercise echocardiography or exercise SPECT imaging? A meta-analysis of diagnostic test performance. JAMA 1998;280:913–20.
[20] Klocke FJ, Baird MG, Lorell BH, Bateman TM, Messer JV, Berman DS, O'Gara PT, Carabello BA, Russell Jr RO, Cerqueira MD, St John Sutton MG, DeMaria AN, Udelson JE, Kennedy JW, Verani MS, et al. ACC/AHA/ASNC guidelines for the clinical use of cardiac radionuclide imaging—executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2003;42:1318–33.
[21] Sánchez CD, Newby LK, Hasselblad V, McNulty SE, Storrow AB, Gibler WB, Garvey JL, Schreiber DH, Tucker JF, Ohman EM. Comparison of 30-day outcome, resource use, and coronary artery disease severity in patients with suspected coronary artery disease with and without diabetes mellitus assigned to chest pain units. Am J Cardiol 2003;91:1228–30.
[22] Froelicher VF, Perdue S, Pewen W, Risch M. Application of metaanalysis using an electronic spread sheet for exercise testing in patients after myocardial infarction. Am J Med 1987;83:1045–54.
[23] Itoh H, Ajisaka R, Koike A, Makita S, Omiya K, Kato Y, Adachi H, Nagayama M, Maeda T, Tajima A, Harada N, Taniguchi K, Committee on Exercise Prescription for Patients (CEPP) Members. Heart rate and blood pressure response to ramp exercise and exercise capacity in relation to age, gender, and mode of exercise in a healthy population. J Cardiol 2013;61:71–8.